Comparison of the pharmacodynamics of imipenem in patients with ventilator-associated pneumonia following administration by 2 or 0.5 h infusion

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Objectives: The aim of this study was to compare the t>MACs of imipenem between administration by a 2 h infusion with a 0.5 h infusion.

Methods: The study was a randomized three-way crossover in nine patients with ventilator-associated pneumonia. Each subject received imipenem in three regimens consecutively: (i) a 0.5 h infusion of 0.5 g every 6 h for 24 h; (ii) a 2 h infusion of 0.5 g every 6 h for 24 h; and (iii) a 2 h infusion of 1 g every 6 h for 24 h.

Results: Following the 0.5 h infusion of 0.5 g of imipenem, the percentages of the t>4×MICs of 4, 2 and 1 mg/L were 20.32 ± 9.32%, 44.11 ± 16.40% and 64.67 ± 20.56% of a 6 h interval, respectively. For the 2 h infusion of 0.5 g of imipenem, the percentages of the t>4×MICs of 4, 2 and 1 mg/L were 17.71 ± 19.27%, 53.75 ± 19.30% and 76.54 ± 17.36% of a 6 h interval, respectively. For the 2 h infusion of 1 g of imipenem, the percentages of the t>4×MICs of 4, 2 and 1 mg/L were 60.26 ± 23.96%, 77.78 ± 20.11% and 93.35 ± 8.26% of a 6 h interval, respectively.

Conclusions: The 2 h infusions of imipenem resulted in greater t>MACs than the 0.5 h infusion. For infections caused by pathogens with high MICs, a 2 h infusion of 1 g of imipenem every 6 h can provide plasma concentrations above the MIC of 4 mg/L for 60% of a 6 h interval.

Keywords: carbapenems, pharmacokinetic/pharmacodynamic, β-lactams

Introduction

Pharmacodynamic (PD) analyses have helped in the development of antibiotic administration regimens that maximize antibacterial effects. Aminoglycosides, for example, have been found to exhibit concentration-dependent bacterial killing, and increasing the peak serum drug concentration enhances the bactericidal activity of these agents.1 On the other hand, the peak serum drug concentration enhances the bactericidal effects. Aminoglycosides, for example, have been found to exhibit concentration-dependent bacterial killing, and increasing the peak serum drug concentration enhances the bactericidal activity of these agents.1 On the other hand, β-lactam antibiotics exhibit primarily time-dependent killing. Therefore, the time that concentrations in tissue and serum are above the MIC (t>MIC) is the pharmacokinetic (PK)/PD index that correlates with efficacy.2,3 and the optimal method to maintain such serum drug concentrations would be to administer the agent by continuous infusion.4–6 Imipenem is a carbapenem antibacterial agent with a broad spectrum of activity.7 In common with other β-lactams, the main PK/PD index that correlates with its therapeutic efficacy is the t>MIC, and administration by continuous infusion is the preferred route to maximize this parameter. However, in tropical countries, the stability of imipenem is an important consideration when continuous infusion is to be used. A previous study showed that imipenem remained 90% stable for <3 h at 37°C and was degraded by up to 60% within 24 h at that temperature.8

We recently conducted a study to compare the PK/PD of imipenem in normal volunteers when it was administered by a 2 or 0.5 h infusion regimen. The study revealed that a 2 h infusion of imipenem gives greater values for t>MIC than a 0.5 h infusion.9 In addition, a 3 h infusion of meropenem and a 4 h infusion of doripenem were also shown to provide greater values for t>MIC than those of a bolus injection.10–12 We have therefore suggested that administration by prolonging the intermittent infusion may offer the opportunity to increase the t>MIC within the limitations of stability at room temperature. An earlier study has demonstrated that free drug is available for antimicrobial activity; however, imipenem has low (<10%) protein binding,13 and therefore, t>MIC for both free and total drug required for bactericidal effect is not much different.

For the treatment of most serious infections, including ventilator-associated pneumonia (VAP), this drug should be...
administered at a dosage of 0.5 g intravenously every 6 h; if necessary, this dosage can be increased to a maximum of 1 g every 6 h. Therefore, the aim of this study was to assess the PD of 0.5 and 1 g of imipenem in patients with VAP following administration by a 0.5 or 2 h infusion. We conducted the study to compare the t\textsuperscript{\textgreater\textless}MICs of imipenem in three regimens: (i) a 0.5 h infusion of 0.5 g; (ii) a 2 h infusion of 0.5 g; and (iii) a 2 h infusion of 1 g.

Materials and methods

Subjects

The study was conducted with patients who were intubated and receiving mechanical ventilation. The patients were eligible for the study if they met the following criteria: (i) older than 18 years; and (ii) clinical suspicion of VAP, defined by a new and persistent infiltrate on chest radiography associated with at least one of the following: purulent tracheal secretions, temperature of 38.3°C or higher or a leucocyte count higher than 10000 cells/mm\textsuperscript{3}. Patients were excluded from the study if they were pregnant or in circulatory shock (which was defined as a systolic blood pressure of <90 mmHg and poor tissue perfusion) or had documented hypersensitivity to imipenem or an estimated creatinine clearance (determined by the Cockcroft–Gault method\textsuperscript{14}) of <60 mL/min. The protocol for the study was approved by the Ethics Committee of Songklanagarind Hospital, and written informed consent was obtained from each subject’s legally acceptable representative before enrolment.

Drugs and chemicals

Imipenem (Tienam\textsuperscript{®}) was purchased from MSD, Thailand. Imipenem was generously donated by Merck & Co, Inc., USA, as pure powder. All the solvents were of HPLC grade.

Study design

The study was a randomized three-way crossover study. Imipenem was reconstituted according to the manufacturer’s guidelines. It was then diluted into two preparations: 0.5 g in 100 mL of normal saline solution and 1 g in 100 mL of normal saline solution. Each subject received imipenem in three regimens at room temperature (32–37°C) consecutively: (i) infusion of 0.5 g of imipenem for 30 min via an infusion pump at a constant flow rate every 6 h for 24 h; (ii) 2 h infusion of 0.5 g of imipenem via an infusion pump at a constant flow rate every 6 h for 24 h; and (iii) 2 h infusion of 1 g of imipenem via an infusion pump at a constant flow rate every 6 h for 24 h. After completion of imipenem therapy for 3 days, all patients were appropriately treated with other antibiotics for 10 days.

Blood sampling

Imipenem PK studies were carried out during administration of the fourth dose of each regimen (18–24 h after the start of each regimen). Blood samples (~3 mL) were obtained by direct venipuncture at the following times: before (time zero) and 0.5, 1, 2, 3, 4, 5 and 6 h after the fourth dose of each regimen. Blood samples were added to the heparinized tube and centrifuged at 1000 g for 10 min but not later than 15 min after collection. An equal volume of stabilizing solution (0.5 M MOPS/water/ethylene glycol, 2:1:1, v/v/v) was added to each plasma sample, vortexed and stored at −80°C until analysis within 1 week.

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Imipenem assay

This assay was used for measuring imipenem concentrations only, not for cilastatin concentrations. The concentrations of imipenem were determined by reversed-phase HPLC. The samples were prepared by the method of Garcia-Capdevila et al.\textsuperscript{15} Briefly, 250 μL of the stabilizing solution was added to 250 μL of the sample. Mixtures were then subjected to ultrafiltration, using Ultrafree\textsuperscript{®}-MC Centrifugal Filter Units, for 10 min at 6000 g. An aliquot of the sample (10 μL) was injected, using an automated injection system (Waters 717 plus Autosampler, Waters Associates, Milford, MA, USA), onto a Nova-Pak C18 column (Waters Associates). The mobile phase was 0.2 M borate buffer, pH 7.2, at a flow rate of 1 mL/min. The column effluent was monitored by UV detection (Waters 486, Waters Associates) at 300 nm. The peaks were recorded and integrated on a Waters 746 Data Module (Waters Associates). The limit of detection of imipenem was 0.125 mg/L.

The intra-assay reproducibility values characterized by coefficients of variation (CVs) were 1.84%, 0.02% and 0.95% for samples containing 1, 10 and 100 mg/L, respectively. The inter-assay reproducibility precision values, calculated by CVs, were 2.60%, 4.75% and 2.18% for samples containing 1, 10 and 100 mg/L, respectively.

PK and statistical analysis

PK analysis was conducted using a non-compartment model. The maximum plasma concentration (C\textsubscript{max}), the minimum plasma concentration (C\textsubscript{min}), the elimination half-life (t\textsubscript{1/2}), the elimination rate constant (k\textsubscript{el}), the area under the concentration–time curve between 0 and infinity (AUC\textsubscript{0–\textinfty}), the total clearance (CL\textsubscript{tot}), and the volume of distribution (V) were determined using WinNonlin Version 1.1 (Scientific Consulting Inc., NC, USA). From the individually fitted concentration–time curves, the time above four times the MIC (t\textsuperscript{\textgreater\textless}MICs) was calculated for MICs of 4, 2 and 1 mg/L. The results were expressed as mean values ± standard deviations, and statistical comparisons were made using the analysis of variance. P values of <0.05 were considered significant.

Results

Nine patients were enrolled in the study. Eight were male and one was female. Their mean age was 63.33 ± 14.86 years (range 33–86) and their mean weight was 66.61 ± 10.44 kg (range 50.5–81.5). The mean plasma imipenem concentrations for 0.5 h infusion of 0.5 g and 2 h infusion of 0.5 g and 1 g are shown in Figure 1. The PK parameters of imipenem for the three

- Plasma concentration of imipenem
- Time (h)

Figure 1. Mean plasma imipenem concentration–time data for nine patients with VAP following administration of: 0.5 g, 0.5 h infusion (filled triangles); 0.5 g, 2 h infusion (filled diamonds); and 1 g, 2 h infusion (filled squares).
regimens are presented in Table 1. The percentages of the $t>4\times$MIC at specific MICs of 4, 2 and 1 mg/L of imipenem after administration of the three regimens are shown in Figure 2. A 2 h infusion of 1 g of imipenem resulted in significantly greater $t>4\times$MIC at specific MICs of 4, 2 and 1 mg/L than those seen after a 2 h infusion of 0.5 g and a 0.5 h infusion of 0.5 g ($P<0.05$, Table 1). A 2 h infusion of 0.5 g of imipenem resulted in significantly greater $t>4\times$MIC at the specific MIC of 1 mg/L than those seen after a 0.5 h infusion of 0.5 g ($P<0.05$, Table 1). All three regimens were well tolerated and there were no reported adverse events.

**Discussion**

An animal study in a murine thigh-infection model has demonstrated that bacteriostatic effects of carbapenems are observed when serum drug concentrations are above the MIC for 20% of the dosing interval, whereas the $t>\text{MIC}$ required for bactericidal activity is 40% of the dosing interval. In addition, optimal killing properties have been observed in critically ill patients when concentrations are maintained at $4\times$MIC. The current study was undertaken to examine the PK/PD of meropenem when administered by a 3 h infusion compared with administration by bolus injection in patients with VAP. A 3 h infusion resulted in greater $t>\text{MICs}$ than those after a bolus injection and a 3 h infusion of 2 g of meropenem every 8 h provided concentrations in serum above $4\times$MIC of 4 mg/L for almost 60% of an 8 h interval. Our previous PK/PD study of imipenem in healthy volunteers found that a 2 h infusion of imipenem resulted in greater $t>\text{MIC}$ values than a 0.5 h infusion, suggesting that a 2 h infusion may be an appropriate route of administration for imipenem in tropical countries and a 2 h infusion of 1 g of imipenem could maintain serum drug concentrations above $4\times$MIC of 4 mg/L for more than 40% of the dosing interval. In this study, we conducted our PK/PD study in critically ill patients with VAP. The mean serum concentrations after a 2 h infusion of 0.5 g of imipenem were above $4\times$MIC of 2 mg/L for 53% of a 6 h dosing interval. Even when a 0.5 h infusion of 0.5 g of imipenem was used, the percentages of time above $4\times$MIC of 2 mg/L were still 44% of the dosing interval. Therefore, from these data, it appears that either a 2 h or a 0.5 h infusion of 0.5 g of imipenem every 6 h can provide serum concentrations above $4\times$MIC of 2 mg/L for more than 40% of the dosing interval. However, a 2 h infusion seems to result in greater $t>\text{MIC}$ values than those seen after a 0.5 h infusion. For pathogens with MICs of 4 mg/L, an imipenem dosage administered through a 2 h infusion should be increased to a maximum of 1 g every 6 h. The mean serum drug concentrations obtained from a 2 h infusion of 1 g of imipenem every 6 h were above $4\times$MIC of 4 mg/L for 60% of a 6 h period. Therefore, only a 2 h infusion of 1 g of imipenem could maintain serum drug concentrations above $4\times$MIC of 4 mg/L for more than 40% of the dosing interval. However, the MIC does not represent an

**Table 1. PK parameters (mean ± SD) of imipenem administered by 2 h and 0.5 h infusion**

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>0.5 h infusion</th>
<th>0.5 g</th>
<th>1 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>34.77 ± 12.19</td>
<td>18.40 ± 4.2$^a$</td>
<td>35.65 ± 9.58$^b$</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (mg/L)</td>
<td>2.01 ± 2.06</td>
<td>2.74 ± 2.23</td>
<td>6.67 ± 6.61</td>
</tr>
<tr>
<td>$k_{el}$ (h$^{-1}$)</td>
<td>0.55 ± 0.17</td>
<td>0.47 ± 0.16</td>
<td>0.55 ± 0.32</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (mg·h/L)</td>
<td>66.68 ± 28.62</td>
<td>67.55 ± 27.53</td>
<td>144.22 ± 73.63$^{a,b}$</td>
</tr>
<tr>
<td>CL$\text{tot}$ (L/h)</td>
<td>8.69 ± 3.27</td>
<td>8.37 ± 2.74</td>
<td>8.12 ± 3.55</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>1.45 ± 0.71</td>
<td>1.64 ± 0.53</td>
<td>1.69 ± 0.96</td>
</tr>
<tr>
<td>V (L)</td>
<td>16.68 ± 5.33</td>
<td>18.19 ± 3.69</td>
<td>15.7 ± 4.69</td>
</tr>
</tbody>
</table>

$%t>4\times$MIC

- $\text{MIC of 4 mg/L}$ | 20.32 ± 9.32 | 17.71 ± 19.27 | 60.26 ± 23.96$^{a,b}$ |
- $\text{MIC of 2 mg/L}$ | 44.11 ± 16.40 | 53.75 ± 19.30 | 77.78 ± 20.11$^{a,b}$ |
- $\text{MIC of 1 mg/L}$ | 64.67 ± 20.56 | 76.54 ± 17.36$^a$ | 93.35 ± 8.26$^{a,b}$ |

$C_{\text{max}}$, maximum plasma concentration; $C_{\text{min}}$, minimum plasma concentration; AUC$_{0-\infty}$, area under the concentration–time curve between 0 and infinity; CL$\text{tot}$, total clearance; $t_{1/2}$, elimination half-life; $k_{el}$, elimination rate constant; V, volume of distribution; $t>4\times$MIC, time that the serum drug concentration was above four times the MIC.

$^aP<0.05$ versus 0.5 h infusion of 0.5 g of imipenem.

$^bP<0.05$ versus 2 h infusion of 0.5 g of imipenem.
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absolute value. The actual MIC may be a concentration somewhere between the lowest test concentration that inhibits the organism’s growth and the next 2-fold lower test concentration. For pathogens with MICs of 4 mg/L, the actual MIC may be anywhere between 4 mg/L and a concentration close to 2 mg/L. Even under the best of controlled conditions, a dilution test may not yield the same endpoint each time it is performed. Generally, the acceptable reproducibility of the test is within one 2-fold dilution of the actual endpoint.

Previous studies in critically ill patients found that the PK of imipenem in this group were different from those of other patient populations. There were inter-individual variations in imipenem plasma concentrations, and it was very difficult to predict the concentrations of this agent in this patient population, resulting in therapeutic failures.\textsuperscript{18,19} Comparison of the mean PK parameters of imipenem administered by 0.5 h infusion between this study and our previous study in normal volunteers\textsuperscript{5} yielded: $C_{\text{max}}$, 34.77 ± 12.19 versus 48.43 ± 5.89 mg/L; $\text{AUC}_{0-\infty}$, 66.68 ± 28.62 versus 63.71 ± 7.44 mg·h/L; $t_{1/2}$, 1.45 ± 0.71 versus 1.32 ± 0.27 h; and $V$, 16.68 ± 5.33 versus 9.41 ± 1.44 L. The imipenem PK parameters in our study estimates for a 0.5 h infusion in patients with VAP were consistent with the previous studies in critically ill patients,\textsuperscript{18,19} but not at high levels. Therefore, critically ill patients are heterogeneous with regard to conditions that may alter drug concentrations in body fluids.

In conclusion, it was found that a 2 h infusion of imipenem resulted in greater $t > \text{MIC}$ values than a 0.5 h infusion and a dosage of 1 g infusion for 2 h could provide serum concentrations above 4×MIC of 4 mg/L for more than 40% of the dosing interval, suggesting that a 2 h infusion of 1 g for every 6 h should be used to treat infections caused by pathogens with an MIC of 4 mg/L.

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Transparency declarations
None to declare.

References